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# Novel cuproptosis related long non-coding RNA signature in oral squamous cell carcinoma prognosis and immunotherapy

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**Abstract**

Cuproptosis, a recently identified copper-dependent regulated cell death, is increasingly recognized for its relevance in cancer biology. In their study, Kong L et al. have developed a four long non-coding RNA (lncRNA) cuproptosis-related prognostic signature that effectively stratifies oral squamous cell carcinoma (OSCC) patients. The study reveals distinct immune microenvironment patterns with implications for immunotherapy response. Their experimental validation of STARD4-AS1 further supports biological relevance. This comment underscores the importance of integrating cuproptosis biology with lncRNA profiling to enhance prognostic accuracy and inform therapeutic strategies in OSCC. It also emphasizes the need for external validation and detailed mechanistic studies to support clinical translation.

**Keywords** Cuproptosis, Oral squamous cell carcinoma (OSCC), Long non-coding RNA (lncRNA), Prognosis, Immunotherapy

## 1 Introduction

Oral squamous cell carcinoma (OSCC) continues to impose high morbidity and poor survival despite multimodal therapies, largely due to intra-tumor heterogeneity and lack of personalised biomarkers [1]. Conventional prognostic systems (e.g., TNM staging) fall short in guiding tailored treatment decisions. Immune checkpoint inhibitors show variable efficacy in OSCC. This highlights the need for accurate biomarkers of both prognosis and immunotherapy response [2].

Excess copper ($Cu^{2+}$) was first shown to induce cell death in the 1980s [3]. Later, $Cu^{2+}$-ionophores were found to transport copper into cells and trigger tumor cell death, leading to their clinical evaluation [3]. In 2022, Tsvetkov et al. defined cuproptosis as a distinct form of regulated cell death [4]. It is different from apoptosis, ferroptosis, autophagy, and necrosis. Cuproptosis depends on mitochondrial respiration and the lipoic acid pathway. In this process, $Cu^{2+}$ binds to lipoacylated TCA-cycle proteins, causing protein aggregation, loss of Fe–S cluster proteins, and proteotoxic stress, ultimately leading to cell death [4]. In cancer, copper has a dual role. Moderate levels promote

tumor growth, angiogenesis, and metastasis, while excess copper induces cytotoxicity through cuproptosis [3]. Tumors with high mitochondrial activity appear more sensitive to this process, suggesting a targetable metabolic vulnerability. Therefore, strategies that modulate copper levels, including $Cu^{2+}$-ionophores and targeted delivery approaches, are being explored to induce cuproptosis in cancer cells [3].

On the other hand, long non-coding RNAs (lncRNAs) are key regulators of gene expression and have been implicated in nearly all hallmarks of cancer, including the modulation of cell death and the tumor immune microenvironment [5]. By linking cuproptosis pathways with lncRNA regulation, the study by Kong L et al. sets out a novel prognostic model for OSCC [6]. The lncRNA signature shows a strong association with tumor mutation burden (TMB), distinct mutational landscapes across risk groups, and, when combined with TMB, provides enhanced prognostic stratification of patient survival.

Using The Cancer Genome Atlas (TCGA) OSCC cohort, the authors identified 1,430 candidate cuproptosis-related lncRNAs (CRLs) [6]. Further, univariate Cox regression, LASSO and multivariate Cox modelling refined this to a four-lncRNA risk signature: STARD4-AS1, AC068700.1, AC114763.1, and AC106900.1 [6]. Patients classified as high-risk had significantly worse overall survival than low-risk. Immune profiling indicated that high-risk OSCC exhibits increased expression of immune checkpoint genes alongside diminished $CD8^+$ T-cell infiltration. Drug-sensitivity modelling suggested distinct predicted IC50 values for drugs between risk groups. Experimental work confirmed that STARD4-AS1 is upregulated in 20 paired OSCC tissues and cell lines, and knockdown boosted proliferation and migration of OSCC cells [6].

This study integrates emerging mechanistic insight, cuproptosis with lncRNA regulatory networks to illuminate a novel vulnerability in OSCC. The four-lncRNA signature evidently captures biologically meaningful variation in tumor copper-mediated metabolic stress and immune microenvironment remodeling. The finding that high-risk patients display immunologically "cold" or checkpoint-enriched phenotypes imply that cuproptosis-linked signalling may shape tumour–immune interplay. The risk model correlates with immune checkpoint expression and predicted drug sensitivity. This suggests that cuproptosis-related lncRNAs may regulate immune evasion pathways. As a result, they may influence patient-specific responses to immunotherapy. This is particularly relevant as OSCC often exhibits an immunosuppressive microenvironment that limits immunotherapy efficacy [7].

## 2 Translational and mechanistic insights

The signature shows translational relevance. (1) It improves prognostic accuracy beyond standard clinicopathological factors. This enables risk-adapted management in OSCC. (2) It may also guide immunotherapy selection. High-risk patients may benefit more from PD-1/PD-L1 blockade, while low-risk patients may avoid overtreatment. (3) The functional role of STARD4-AS1 suggests potential for targeting lncRNAs or modulating copper pathways. (4) Drug sensitivity analysis also supports its use in personalized therapy. Conceptually, the association with immune checkpoint expression suggests that these lncRNAs may link metabolic stress with immune signaling. They may influence antigen presentation, oxidative stress, and cytokine pathways. Thus, cuproptosis-related

**Table 1** Differential expression of cuproptosis-related lncRNAs in OSCC

| Name | $Log_2$ fold change | *P*-value |
|---|---|---|
| STARD4-AS1 | 2.12 | 2.34E–56 |
| AC068700.1 | 2.46 | 2.05E–40 |
| AC114763.1 | 0.44 | 0.47 |
| AC106900.1 | Not detected | – |

lncRNAs may represent a regulatory axis connecting copper metabolism, mitochondrial function, and tumor–immune interactions in OSCC.

## 3 Critical evaluation and limitations

While the four-lncRNA signature demonstrates promising predictive performance, several limitations warrant consideration. The observed association with immune checkpoint expression remains largely correlative and lacks mechanistic validation. Dependence on bulk TCGA transcriptomic data may obscure cell-type–specific expression patterns and introduce batch effects, while the retrospective design may introduce cohort bias and fail to capture temporal tumor evolution and intratumor heterogeneity.

Our RNA-seq analysis comparing OSCC tissues with adjacent non-tumor samples ($n = 3$) revealed significant overexpression for STARD4-AS1 and AC068700.1 (Table 1), further supporting their potential relevance in OSCC biology. However, functional validation was restricted to STARD4-AS1, and the biological relevance of the remaining lncRNAs remains unclear. In addition, the absence of external validation cohorts and reliance on in silico drug sensitivity predictions limit the translational robustness of the findings.

## 4 Future research roadmap

Future work should: (1) validate the model prospectively across multicentre OSCC cohorts and diverse populations; (2) mechanistically dissect each lncRNA, especially how they regulate copper transport, mitochondrial lipoylation or immune checkpoint expression; (3) deploy multiomics (metabolomics, single-cell RNA-seq, spatial transcriptomics) to situate the signature in tumor micro-environment context; (4) conduct preclinical interventional studies combining lncRNA knockdown or copper-modulation with immune-checkpoint therapy. Given that cuproptosis is implicated across cancers (e.g., lung, renal, gastric) and non-malignant copper-related disorders (e.g., Wilson's disease), the translational relevance of these findings extends well beyond OSCC [3, 8].

In conclusion, The study by Kong L. et al. advances OSCC research by integrating cuproptosis into prognostic modeling. The lncRNA signature links copper dysregulation with tumor behavior and immune interactions, offering added predictive value. While promising for risk stratification and personalized therapy, further validation and mechanistic studies are needed before clinical application. More broadly, cuproptosis may represent a therapeutic vulnerability across cancers.

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**Author contributions**
SS is the sole author and was responsible for the original drafting, writing, review, editing, and submission of the manuscript.

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**Data availability**
All data generated in this study are included within the manuscript.

## Declarations

**Ethics approval and consent to participate**
This comment is based on the published study by Kong L. et al. (2025) [6]. The RNA-seq analysis presented in Table 1 was conducted with approval from the Institutional Ethics Committee [DYPV/EC/910/23, dated 23/01/2023] of Dr. D. Y. Patil Biotechnology and Bioinformatics Institute, Dr. D. Y. Patil Vidyapeeth (DPU), Pune, India. All samples were collected following informed consent.

**Consent for publication**
I agree to publish.

**Competing interests**
The author declares no competing interests.

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